# Stress and drug addiction: an up-to-date perspective from 2020

## *Estrés y drogadicción: una perspectiva actualizada para 2020*

Anna Wojdala*, Francisco Molins*, Miguel Ángel Serrano*.

* Department of Psychobiology. University of Valencia, Valencia. Spain.

The problem of drug addiction treatment remains an important problem of society and is subject to advanced research. Discovery of mechanisms driving process of drug addiction seems to be an obvious step on the way to problem solution. Majority of researchers' attention seems to be paid for brain disease model of drug addiction. We suggest, that parallel to studies centered on brain disease model, more attention should be paid to research addressed to the key role of psychosocial factors and stress in emergence and further progressing of drug addiction (Ruisoto & Contador, 2019).

However, a broad and comprehensive perspective is needed in order to bring closer the labor of researchers and therapists. In this sense, the "integration of neuroscience with multiple disciplines (cognition, behavior and contextual in-fluences) holds potential to create new avenues for the application of process-oriented interventions and guidelines for clinical psychological practice" (De Raedt, 2020, p. 35).

In this editorial, using a neuroscientific approach, we highlight main matters of concern of currently ongoing research in relation to addiction and stress and point to possible future research directions which could bring valuable contribution in our knowledge about addictions.

Based on three comprehensive up-to-date review articles (Andersen, 2019; Koob & Schulkin, 2019; Ruisoto & Contador, 2019) addressing a contribution of stress in vulnerability to drug addiction and its development, we claim that the role of stress is multi-levelled. Stress seems to be an important factor both for vulnerability to onset, development, risk of relapse and treatment of addiction and, should be considered as impacting all stages of addiction (binge/intoxication, withdrawal/negative affect, preoccupation/anticipation).

Thus, it has been suggested recently (Koob & Schulkin, 2019) that question of stress in drug addiction fits with an allostatic model and should be considered with regard to this model. Allostasis is a term proposed over 30 years, however its meaning is still subject to discussion (Schulkin & Sterling, 2019). Allostasis is usually presented as a way of achieving stability through change (McEwen & Wingfield, 2003). In contrast to homeostasis, specified by negative feedback, allostasis functioning is based on feed-forward mechanisms (Koob & Schulkin, 2019). In terms of stress, allostasis could be described as an "adaptation in the face of potentially stressful challenges" (McEwen, 1998, p. 33) which "(…) involves activation of neural, neuroendocrine and neuroendocrine-immune mechanisms (McEwen, 1998, p. 33). Following allostatic model, Koob and Schulkin (2019) suggest, that stress is supposed to create an emotional allostatic load and allostatic state, what eventually leads to pathological dysregulation of motivational neurocircuits and addiction. Authors claim, that allostatic changes strongly influence the hedonic reward systems to drive compulsive drug seeking via the construct of nega-

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**Send correspondence to:**
Miguel Ángel Serrano. Department of Psychobiology. University of Valencia. Avda. Blasco Ibañez, 21. 46010 Valencia (Spain)
Phone: 963 983 456. Email: maserrar@uv.es

tive reinforcement (Koob & Schulkin, 2019). One of the primary (but not sole) mediators of allostasis is hypothalamic-pituitary-adrenal (HPA) axis (McEwen & Wingfield, 2003), which is the main stress response system (Dunlavey, 2018). There is a great number of molecules binding issues of addiction and stress, however corticotropin-releasing factor (CRF), being closely related to functioning of HPA axis, seems to be an especially important candidate for further investigation. A key point of future research should be a full evaluation of changes which CRF undergoes in the brain exposed to drug and stress, especially in areas of HPA axis, extended amygdala and prefrontal cortex. Staying in line with suggestion of Koob and Schulkin (2019), allostatic conception appears to be the right direction of further research, enabling to track all stages of transition leading to addiction.

Referring to recent review of Ruisoto and Contador (2019), a noteworthy aspect of addiction research is the question of careful translation of animal studies in drug addiction to humans. Authors underscore, that majority of studies conducted with use of animals evidently limit importance of psychosocial stressors. Thus, future investigation regarding human drug addiction ought to strongly consider psychosocial factors, guaranteeing proper validity (Ruisoto & Contador, 2019). Also, evaluation of individual differences between susceptibility and resilience to stress should be taken under advisement. Another key point of future studies could be a focus on similarities between impact of stress in drug-addiction and other - non-drug/behavioral - addictions, resembling some of the neurobiological mechanisms described in drug addiction (Ruisoto & Contador, 2019). Stress can induce long-term brain changes, similar to these occurring in brain after exposure to drug. Such information suggest that reduction of stress level may significantly improve effectiveness of drug addicts' treatment. Different approaches are proposed to help in treatment, including social support, physical exercise, contingency management, mindfulness treatments or encouraging to non-drug alternative reinforcers for pleasure-seeking or stress-relief (Ruisoto & Contador, 2019). Such a line, incorporated in social policies, could become not just a method of treatment but possibly an effective method of prevention.

An extremely interesting issue of the role of stress in drug addiction was raised in a review of Andersen (2019), underscoring the impact of stress experience occurring in early postnatal life on risk of drug dependence development. In the same line, Bousoño et al. (2019) recall that experiencing stress in form of parental problems, abuse or abandonment during childhood is correlated with later problems in adolescence (both at school and with peers) that, in turn, increase risk of early age drug abuse. It is known that early life stress experience correlates with an accelerated age of drug use onset and also higher vulnerability to drug dependence. Earlier onset of drug abuse correlates with long-lasting addiction (Andersen, 2019). Therefore, as recently it has been stated from a preventive point of view, there is a need to reinforce family prevention in general and the role of parents in particular (Rial et al., 2019). As mentioned by Ruisoto and Contador (2019), developing brains are more vulnerable to the toxic effects of exposure to stress hormones associated with practically every form of stress experiences – beginning from both psychological and physical abuse, through neglect and poverty to major sources of the allostatic load. Such experiences lead to long-term changes in brain.

Understanding of influence of stress occurring in early life (not only during adulthood or adolescence) on vulnerability to addiction onset, prior to emergence of symptoms, seems to be crucial in context of effective prevention.

Elucidation of how experience of stress influences future vulnerability to drug abuse and addiction, with regard to time of emergence of stress, its intensity and duration, remains a challenge and should be subject to further long-lasting research. Future investigations focused on correlation between stress and drug addiction, should have regard to factors such a time of occurrence, duration and type of stressor, as well as sensitive period, age and gender.

Going step further than early postnatal stress, another intriguing issue seems to be a question of inheritance of epigenetic changes provoked by stress. By recalling number of animal and human studies, some authors (e.g. Matthews & Phillips, 2012) claim that prenatal stress can lead to transgenerational effects on stress physiology and behaviors. These findings let to speculate about correlation between inheritance of stress-caused epigenetic changes and vulnerability to addiction. Continuation of the research concerning epigenetic aspects of stress could deliver an interesting information, helpful for (very) early prevention actions.

Following cases of elevated neuroimmune function in individuals with an addiction, Andersen (2019) proposed an idea of potentially pre-exiting condition of inflammation, being result of early life stress exposure, and its impact on drug addiction vulnerability (Andersen, 2019; Frank, Watkins & Maier, 2017). Mentioned article covers also subject of sensitive periods and their relationship to addiction, suggesting need of extensive studies exploring changes undergoing in brain neurochemistry (especially PV, BDNF and its receptor TrkB, and glutamate) while exposure to stress during sensitive periods should be taken into consideration (Andersen, 2019). Full understanding of mentioned changes would be helpful for development of specific treatment.

Different approaches of prevention are proposed (Andersen, 2019), including both existing as well novel pharmacotherapies, applied prior to emergence of symptoms. Suggestions of treatment applied before occurrence of

symptoms are reduction of, recalled above, inflammation, and actions aimed to reduce glutamate activity or increase GABA/PV and/or BDNF level (Andersen, 2019). The key aspect of future studies seems to be proper timing of intervention. Noticing that early postnatal stress experience has occurred and application of immediate prevention treatment without waiting for development of potential addiction may be the case for effective counteracting. In this sense, another key point for addiction prevention in frames of early stress life experience seems to be social buffering expressed by parental care (especially in childhood) and peer support (particularly in adolescence) (Andersen, 2019).

In conclusion, addiction research should take into account aspect of stress experiences in different ways, having regard to:

- allostatic model of drug addiction,
- role of CRF in regard to stress and vulnerability to addiction,
- deliberative translation of animal studies to human beings, especially, considering role of psychosocial factors and individual differences,
- impact of stress on drug-addiction and other (behavioral) addictions,
- studies on the long-term brain changes affected by stress aimed to improve effectiveness of drug addict's treatment,
- early stress experience in prenatal and postnatal life and its effect on vulnerability to addiction onset,
- and proper timing of intervention depending on the moment of stress exposure.

Therefore, the impact of stress on drug addiction is certainly a complicated issue, implicating both physical (brain disease) and psychosocial factors leading to occurrence of addiction, its development and relapse. An interdisciplinary research, making use of the advances of neuroscience, concerning different aspects of the problem, seems to be a promising approach. A proper understanding of the mechanisms driving to addiction is crucial for wellbeing of society, enabling correction of existing social policies.

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